REMARKS

Applicant respectfully requests reconsideration. Claim 19 was previously pending in this application. Claim 19 has been amended herein. New claims 20-25 are added. As a result, claims 19-25 are pending for examination and claim 19 is an independent claim. Claim 19 was amended to add further structural limitations to the claims including the formula 5' $X_1X_2CGX_3X_4$ 3', a size limitation and a phosphorothioate linkage. No new matter has been added.

Applicant appreciates the Examiner's indication that prior rejections are withdrawn.

Rejection Under 35 U.S.C. 112

Claim 19 has been rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating an allergic response to an antigen or allergy related disorder during antigen specific immunotherapy of a subject comprising administering to a subject during antigen specific immunotherapy a composition comprising CpG, SEQ ID NO: 10 and antigen (administering a first and second composition), does not reasonable provide enablement for treating an allergic response to any antigen comprising administering to a subject during antigen specific immunotherapy any immunostimulatory oligonucleotide CpG, of any size and an antigen (administering a first and second composition).

The specification provides sufficient guidance for one of ordinary skill in the art to practice the claimed invention. The specification describes a class of oligonucleotides having a common structural motif (i.e., an unmethylated CG dinucleotide in a 6 mer sequence) that, when administered to a subject, results in alteration of the immune response in the subject, with a Th1 immune response being favored. This class of oligonucleotides is described throughout the specification, and its ability to produce a Th1 favored immune response is not only described (e.g., see page 8, lines 11-16 and pages41-42) but *in vitro* and *in vivo* data are also presented using an adequate number of different CG oligonucleotides to meet the enablement requirement for the claimed invention. Page 41 of the specification describes how a shift from a Th2 response, associated with IgE antibody production to a Th1 immune response is useful in the treatment of allergy.

The data in the application, including those presented in Tables 1-3, establish that the structural motif common to all members of the oligonucleotide class (i.e., the unmethylated CG dinucleotide in a 6 mer sequence) is responsible for the immune response induced by these oligonucleotides. The specification teaches that methylation or mutation of the CG dinucleotide eliminates the immune stimulation profile (e.g., see page 18, lines 21-27, and Table 1).

The immune stimulation data presented in the specification were derived from the use of several CG oligonucleotides. Tables 1-3 describe immune stimulation of murine cells by at least 35 CG oligonucleotides. Tables 1-3 demonstrate that many different CG oligonucleotides are capable of activating murine B cells and inducing cytokine expression in murine cells *in vitro*. Table 5 describes immune stimulation of human cells by 11 different CG oligonucleotides. Table 5 demonstrates that several CG oligonucleotides are capable of inducing cytokine expression and notably an IL-12 response in human cells in vitro.

The Examiner emphasizes Example 12 as evidence that a method for treating asthma using a CG oligonucleotide comprising SEQ ID NO:10 is enabled. Example 12 is a model of allergic asthma, a subset of allergy and asthma. Applicant stresses that the specification provides teachings in addition to those in Example 12, and these data when taken together support the class of CG oligonucleotides in the treatment of allergy. As described above, the specification provides a variety of data that evidence immune stimulation by many CG oligonucleotides, and not simply those comprising SEQ ID NO:10.

Applicant wishes to clarify a statement made by the Examiner in the instant Office Action. The Examiner states, with respect to Example 12, that SEQ ID NO:10 was administered to immunized mice. Example 12 describes an experiment in which mice were administered Schistosoma mansoni eggs either with or without CG oligonucleotide in order to sensitize the mice. Mice were not immunized with Schistosoma mansoni eggs and then administered CG oligonucleotides.

According to the Examiner, the specification does not enable the use of oligonucleotides of less than 8 nucleotides. Although Applicant disagrees with the rejection, in order to advance prosecution claim 19 has been amended to recite a minimal length of 8 nucleotides. The Examiner cited Yamamoto et al. (1994) to support her position that relatively short oligonucleotides are

inactive. Applicant respectfully contends that the teaching of the Yamamoto reference is taken out of its context. In the Brief Communication, Yamamoto et al. examined 13 oligonucleotides of various length, in the context of the AACGTT hexamer. Among the 13 oligonucleotides tested, only three were 16 nucleotides or less in length. Based on this, the authors concluded "the oligonucleotides 16 bases or less in length were not active" (abstract). Give the limited scope of the study, such conclusion should be construed only in the narrow context in which the study was conducted to reflect. The data presented in Yamamoto et al. are insufficient to support a broad notion that *no* oligonucleotides 16 or shorter in length are immunostimulatory, as suggested by the Examiner. Further studies by Dr. Yamamoto showed a very different result. Sonehara et al., J. Interferon cytokine Res., 1996, 16:799-803 showed that using lipofectin, oligonucleotides as short as 6 nucleotides long are immune stimulatory. Interestingly, the oligonucleotides were also phosphodiester. Other later evidence also suggests shorter oligonucleotides are immune stimulatory. For example, specific examples of immunostimulatory CpG oligonucleotides that are 6 nucleotides or shorter are described in U.S. Patent Application 11/361,313 (see, for example, Table 3), which teaches oligonucleotides of 2 to 7 nucleotides in length. Thus, the evidence is sufficient to rebut the teachings of Yamamoto et al. to the extent that they are viewed as supporting a lack of enablement.

The Examiner states that accessible target sites, modes of delivery and formulations of the claimed oligonucleotides would have to be determined de novo in order to practice the claimed invention. Applicant respectfully disagrees. The Examiner has provided no basis for, nor is there any reason to expect, a difference in target sites, delivery routes, and formulations of CG oligonucleotides in the claimed method.

The Examiner asserts that treatment using CG oligonucleotides is unpredictable, and cites a number of references to support this position. Each of these references is discussed below.

The Examiner cites Weiner (J. Leukocyte Biology, 2000, 68:456-463) for the proposition that the molecular mechanism of CG oligonucleotide immunostimulation is unknown. Respectfully, knowledge of the mechanism of action is not required for patentability. Notwithstanding this, a detailed knowledge of the cellular effects of CG oligonucleotides was available at the effective filing date and was described in the specification. The specification identifies consistent changes in

the immune system at the cellular level that occur in response to CG oligonucleotide administration and that are therapeutically relevant. Additionally, Table 1 of the Weiner reference lists examples of cellular effects arising from immunostimulatory CG oligonucleotides. A lack of understanding of the molecular mechanism does not render these cellular results unpredictable. Other statements in the reference are consistent with enablement of the claimed invention. For instance, it is taught on page 456 1st column, second full paragraph, that "Studies to date suggest CpG DNA could have significant therapeutic promise in the treatment of a variety of disorders, including infectious disease, allergy, and cancer." It is further taught on page 457 under "In vivo effects of CpG ODN" that "extensive studies have been done in rodents, and some studies have been done in non-human primates. The observed *in vivo* data fits well with the *in vitro* data outlined above."

Agrawal et al. (Molecular Med. Today 2000, 6:72-81) is cited in support of the proposition that the incorporation and positioning of chemical modifications relative to the CG dinucleotide are highly unpredictable. The Examiner has identified pages 78-80 as being particularly relevant. Agrawal et al. is a review article describing antisense oligonucleotides. The reference suggests on page 78 that in order to reduce non-antisense related activity it is best to avoid CpG motifs. The reference also suggests three modifications to reduce CG related activity when it is not possible to eliminate CG dinucleotides altogether. One of the suggested modifications is replacement of the cytosine base of the CG dinucleotide with a 5-methyl cytosine base. This contrasts with the instant claims which recite a CG oligonucleotide having an unmethylated C in the CG dinucleotide. Further, the cited section of Agrawal et al. teaches that the suggested modifications "significantly reduced side effects". Agrawal et al. does not teach that immune stimulation was abolished with any of these proposed modifications, just reduced. The reference as a whole stands for the proposition that unmethylated CG dinucleotides and oligonucleotides containing them are immunostimulatory.

The Examiner further asserted that "there is no evidence of record that any sequence that is not fully phosphorothioated provides for immune stimulation in any model" and cited Zhao et al. In fact, earlier observations that bacterial DNA, but not mammalian DNA, can stimulate immune response, provide evidence that immunostimulatory nucleic acid molecules do not have to be fully phosphorothioated. Phosphodiester oligonucleotides are tested in the specification in Example 10

and showed immune stimulatory capacity although reduced compared with modified oligonucleotides. In addition, there are some examples of immunostimulatory oligonucleotides that are not fully modified with phosphorothioate and still exhibit stimulatory effects. For instance see pages 31 and 19., lines 1-15 as well s Example 10. As described in the specification, phosphorothioate-modified CpG oligonucleotides may be more potent, but that does not in itself mean that unmodified (phosphodiester) oligonucleotides are not immunostimulatory. As mentioned above, Sonehara et al describe an immune stimulatory effect using phosphodiester oligonucleotides. Further, in order to advance prosecution Applicant has amended the claim to add the limitation that the oligonucleotide include at least one phosphorothioate linkage.

Based on the guidance provided by the specification and the state and predictability of the art at the time of the invention, the amount of experimentation needed to practice the claimed invention does not exceed that amount routinely engaged in by a person of ordinary skill in the art.

Reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting Rejection

Claim 19 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-11 and 13-30 of copending Application No. 09/818918. US 09/818918 has now been abandoned and the claims were filed in US 11/598,207, now pending, in order to correct an inventorship issue. Applicants defer rebuttal of the rejection until allowable subject matter is identified.

Applicant notes that each of US 10/921,086, 09/337,584 (currently in interference), 10/743,625, 10/769,282, 10/817,165, 10/831,778, 10/831,647, 10/831,775, 10/847,642, US 10/888,785, 11/296,572, 11/526197, 10/894657; 11/134,918; 11/598,207 each have a common inventor and include claims directed to various methods of treating asthma or allergy.

US Patent Application 10/099512

Applicants wish to bring to the Examiner's attention that US Patent Application 10/099,512 has been abandoned and no child applications have been filed, according to public PAIR. The

claims of the instant patent application were filed to copy the claims of US Patent Application 10/099,512. Since the subject matter has been abandoned, Applicant is able to amend the pending claims. Applicant believes that the Examiner may not need to consider the pending claims for an Interference with US 10/099,512.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

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Respectfully submitted,

By _____

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